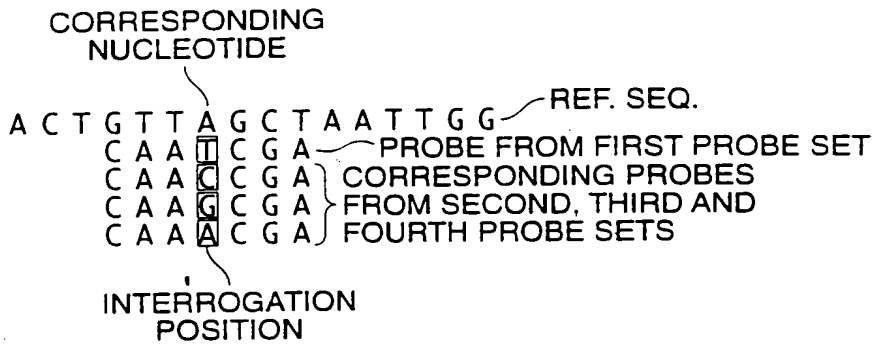
CORRESPONDING NUCLEOTIDE
A C T G T T A G C T A A T T G G
REF. SEQ.
C A A T C G A
PROBE FROM FIRST PROBE SET
C A A C C G A
C A A G C G A
C A A A C G A
CORRESPONDING PROBES FROM SECOND, THIRD AND FOURTH PROBE SETS
INTERROGATION POSITION

FIG. 1

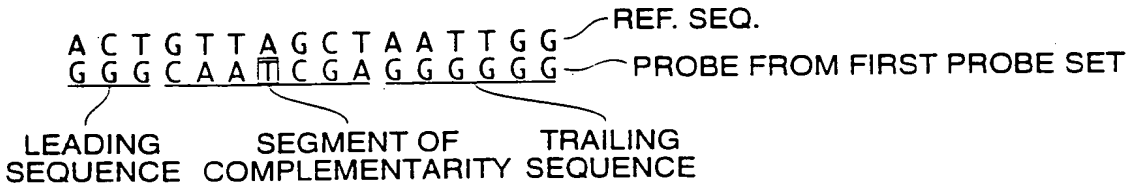
A C T G T T A G C T A A T T G G
REF. SEQ.
G G G C A A T C G A G G G G G G
PROBE FROM FIRST PROBE SET
LEADING SEQUENCE
SEGMENT OF COMPLEMENTARITY
TRAILING SEQUENCE

FIG. 2

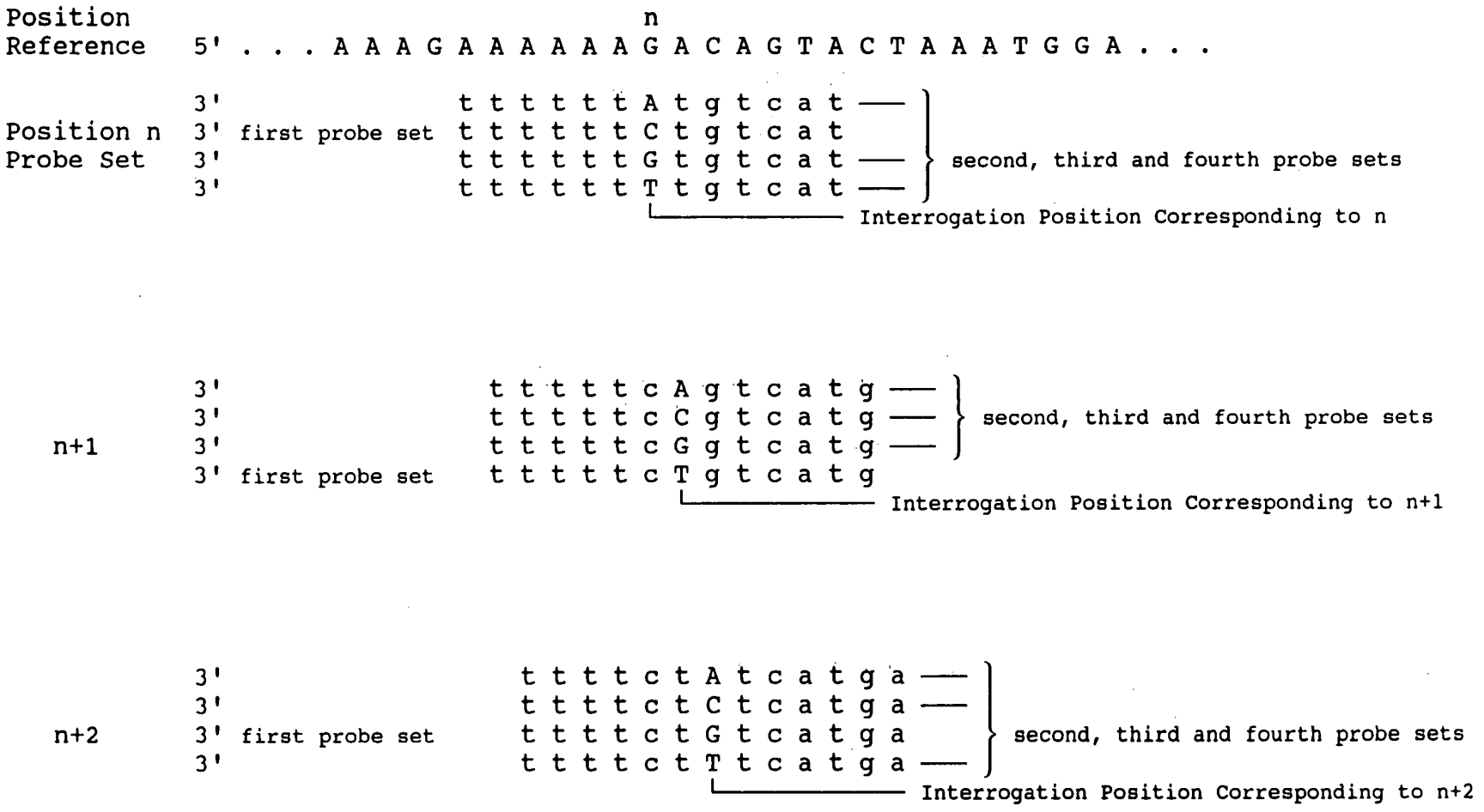
Position
Reference 5' . . . A A A G A A A A A A G A C A G T A C T A A A T G G A . . .
n
3' t t t t t t A t g t c a t —
Position n 3' first probe set t t t t t t C t g t c a t
Probe Set 3' t t t t t t G t g t c a t —
3' t t t t t t T t g t c a t —
second, third and fourth probe sets
Interrogation Position Corresponding to n
3' t t t t t c A g t c a t g —
3' t t t t t c C g t c a t g —
n+1 3' t t t t t c G g t c a t g —
3' first probe set t t t t t c T g t c a t g
second, third and fourth probe sets
Interrogation Position Corresponding to n+1
3' t t t t c t A t c a t g a —
3' t t t t c t C t c a t g a —
n+2 3' first probe set t t t t c t G t c a t g a
3' t t t t c t T t c a t g a —
second, third and fourth probe sets
Interrogation Position Corresponding to n+2

FIG. 3

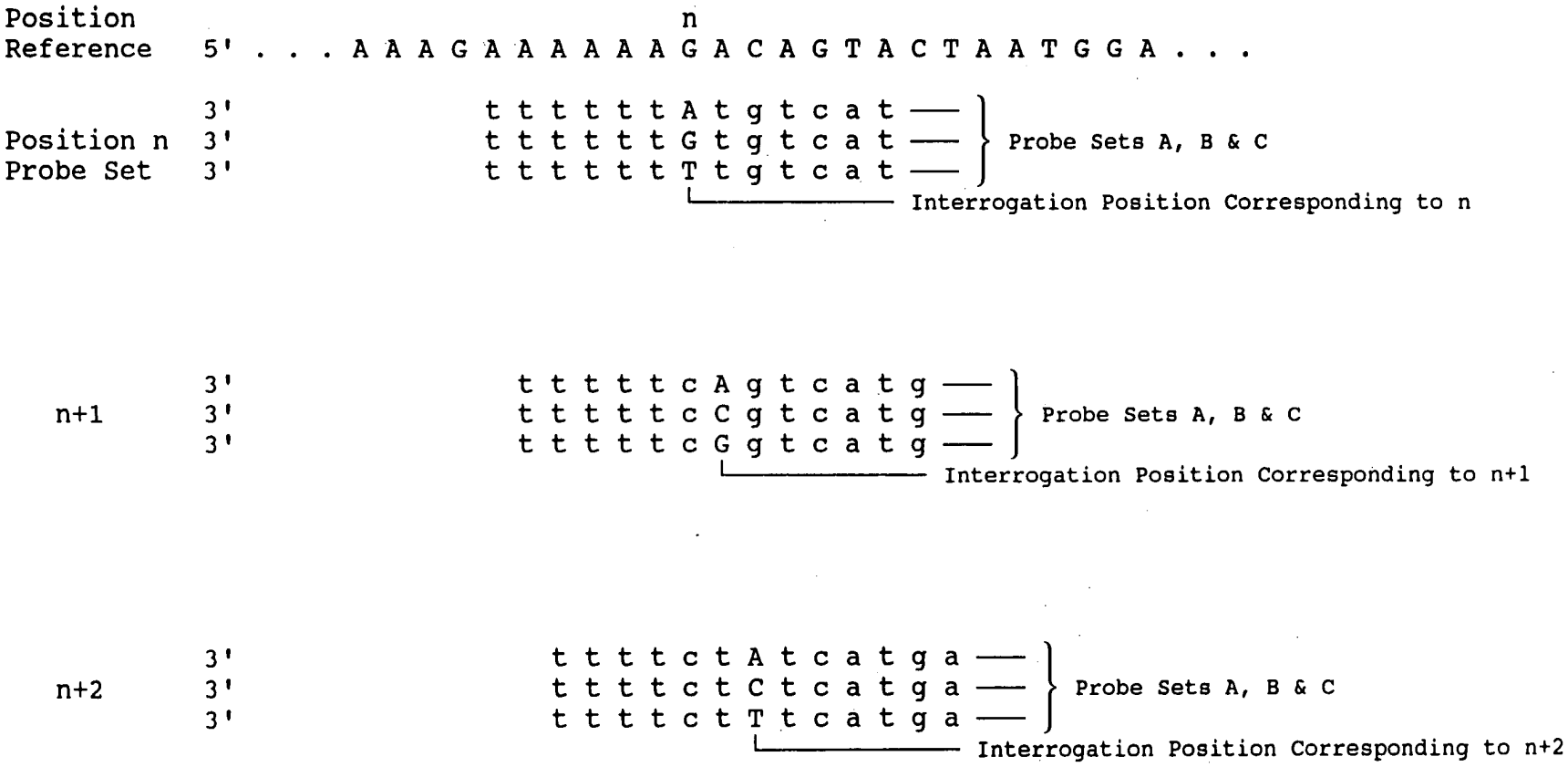
Position
n
Reference 5' . . . A A A G A A A A A A G A C A G T A C T A A T G G A . . .
3' t t t t t t A t g t c a t —
Position n 3' t t t t t t G t g t c a t —
Probe Set 3' t t t t t t T t g t c a t —
Probe Sets A, B & C
Interrogation Position Corresponding to n
3' t t t t t c A g t c a t g —
n+1 3' t t t t t c C g t c a t g —
3' t t t t t c G g t c a t g —
Probe Sets A, B & C
Interrogation Position Corresponding to n+1
3' t t t t c t A t c a t g a —
n+2 3' t t t t c t C t c a t g a —
3' t t t t c t T t c a t g a —
Probe Sets A, B & C
Interrogation Position Corresponding to n+2

FIG. 3B

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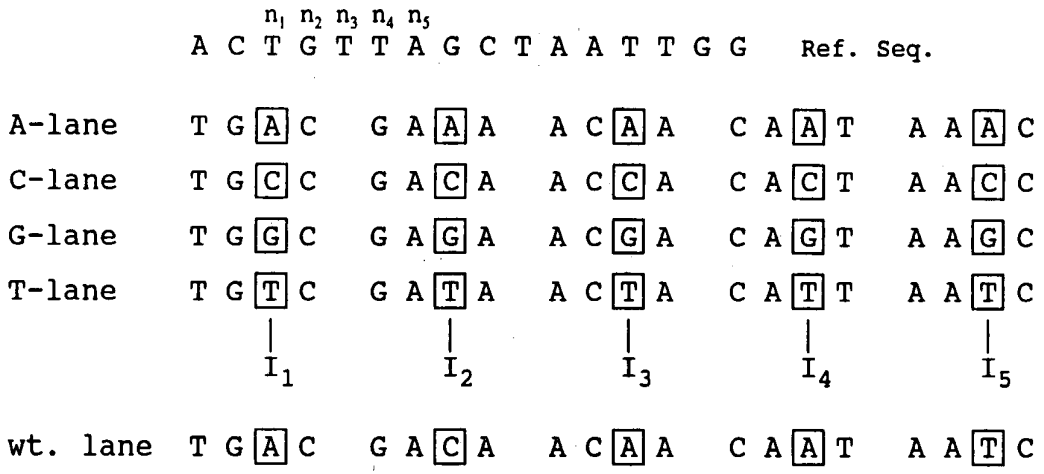

n1 n2 n3 n4 n5
A C T G T T A G C T A A T T G G Ref. Seq.
A-lane T G A C G A A A A C A A C A A T A A A C
C-lane T G C C G A C A A C C A C C A T A A C C
G-lane T G G C G A G A A C G A G G A T A A G C
T-lane T G T C G A T A A C T A C A T T A A T C
I1 I2 I3 I4 I5
wt. lane T G A C G A C A A C A A C A A T A A T C

FIG. 4

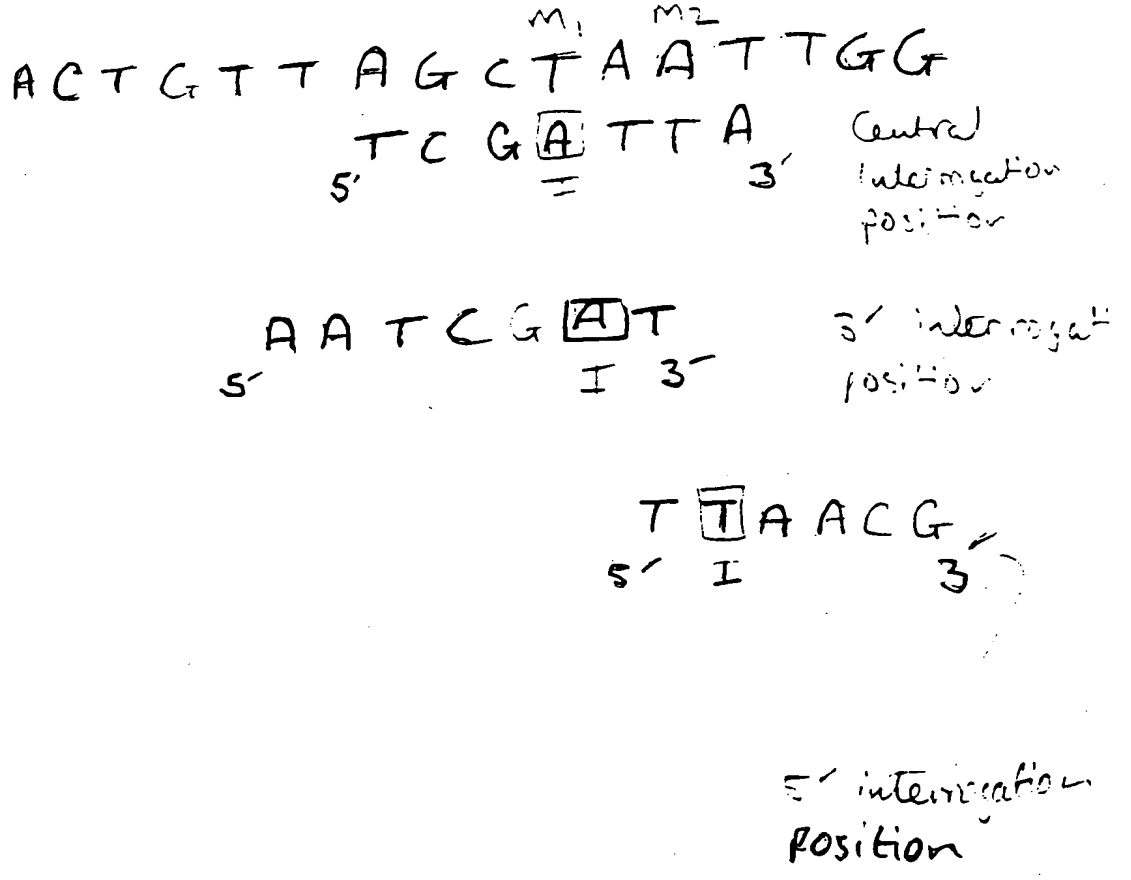

M1
M2
ACTGTTAGCTAATTGG
TCGATTA
5'
3'
Central interrogation position
AATCGAT
5'
I 3'
5' interrogation position
TTAACG
5'
I
3'
5' interrogation position

Fig. 4B

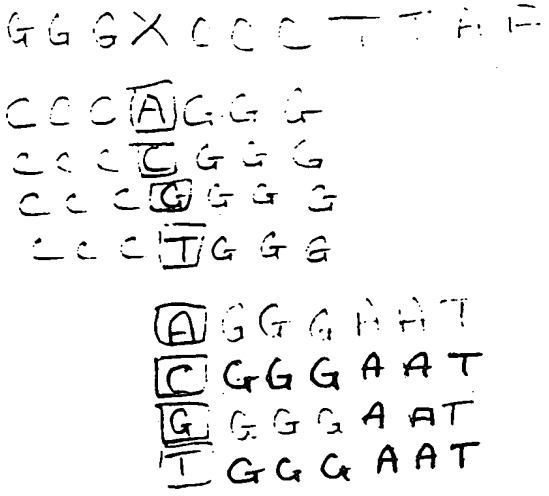


Fig. 4C

Fig. 5

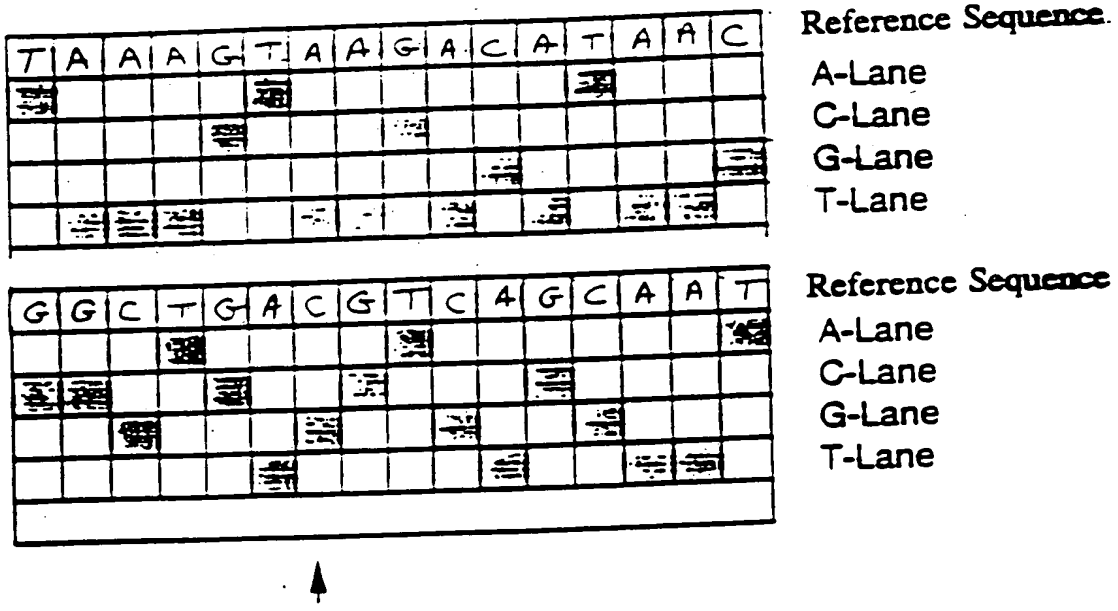


FIG. 5 : Tiled Array with Probes for the Detection of Point Mutations

3'-CCGACTACAGTCGTT
3'-CCGACTCCAGTCGTT
3'-CCGACTGCAGTCGTT

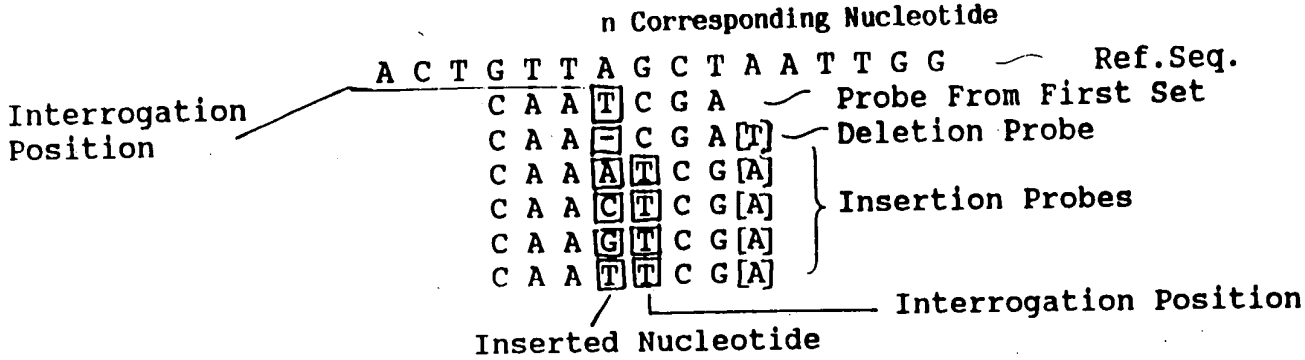

n Corresponding Nucleotide
A C T G T T A G C T A A T T G G
Ref.Seq.
Interrogation Position
C A A T C G A
Probe From First Set
C A A - C G A [T]
Deletion Probe
C A A A T C G [A]
C A A C T C G [A]
C A A G T C G [A]
C A A T T C G [A]
Insertion Probes
Interrogation Position
Inserted Nucleotide

FIG. 6

XX/XX

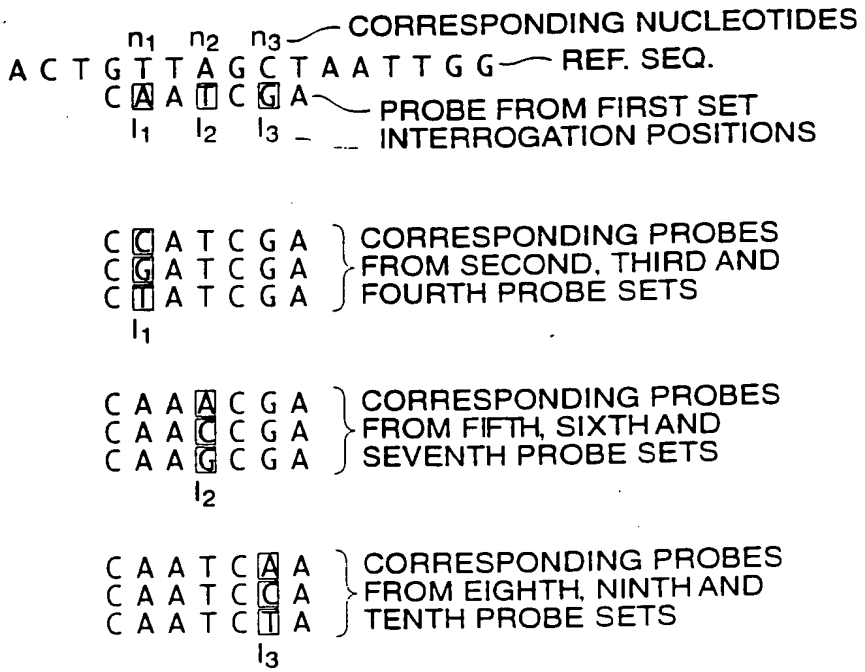

n1 n2 n3
CORRESPONDING NUCLEOTIDES
A C T G T T A G C T A A T T G G
REF. SEQ.
C A A T C G A
PROBE FROM FIRST SET
I1 I2 I3
INTERROGATION POSITIONS
C C A T C G A
C G A T C G A
C T A T C G A
CORRESPONDING PROBES FROM SECOND, THIRD AND FOURTH PROBE SETS
I1
C A A A C G A
C A A C C G A
C A A G C G A
CORRESPONDING PROBES FROM FIFTH, SIXTH AND SEVENTH PROBE SETS
I2
C A A T C A A
C A A T C C A
C A A T C T A
CORRESPONDING PROBES FROM EIGHTH, NINTH AND TENTH PROBE SETS
I3

FIG. 7

XX/XX

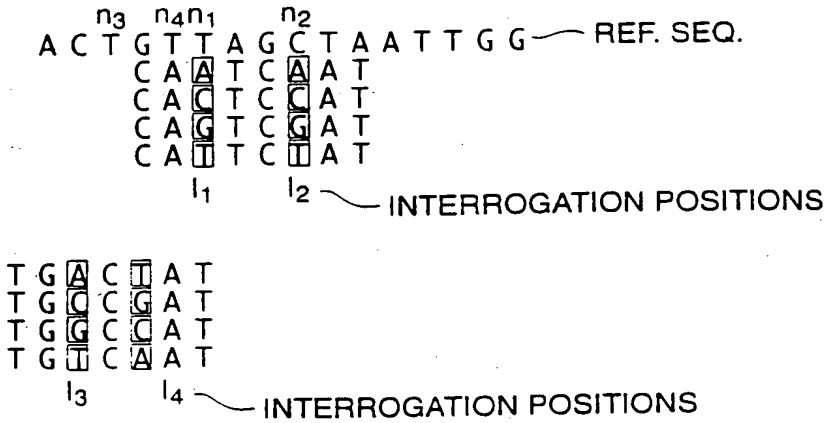


FIG. 8

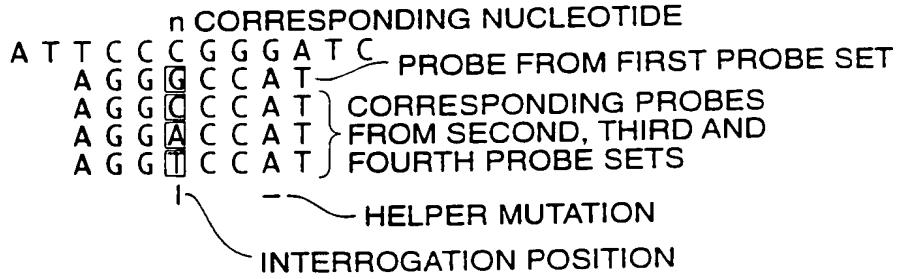
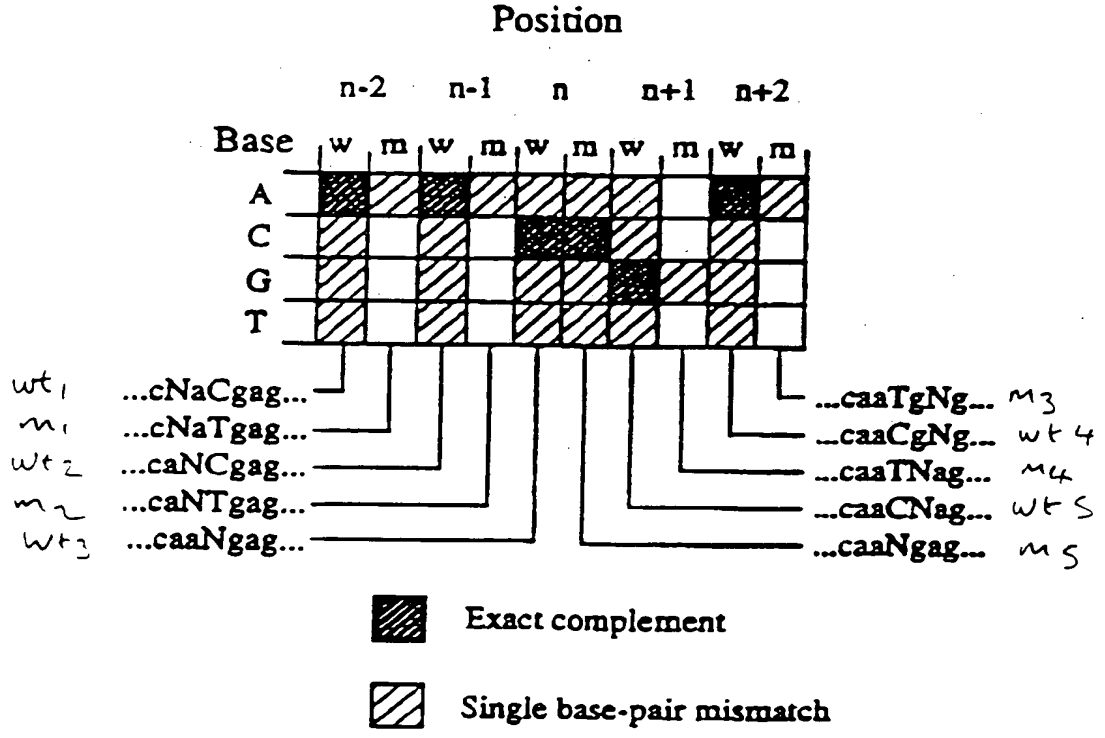


FIG. 9

Array Design for the R553X Point Mutation

Wild-Type Pattern



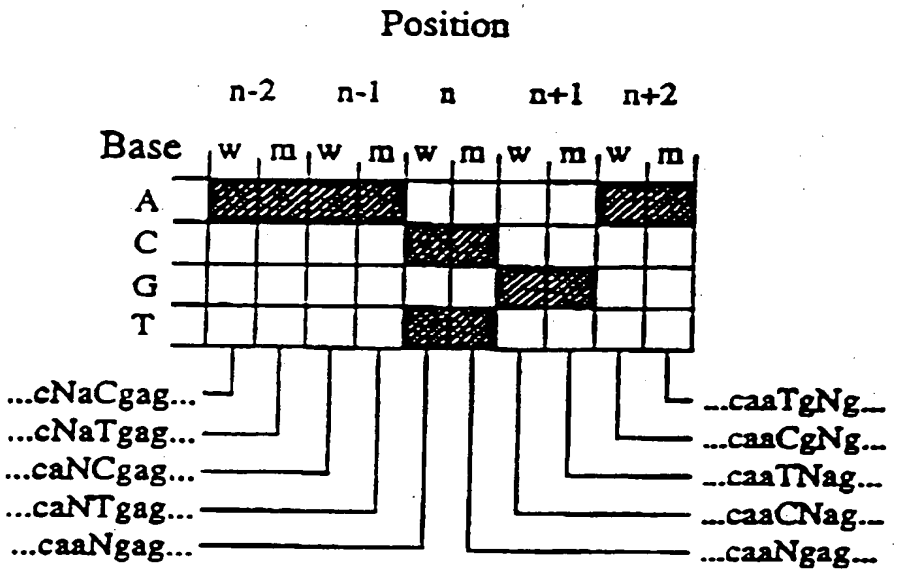
Wild-Type Sequence: 5'-AGGTCAA**C**GAGCAA-3'

Mutant Sequence: 5'-AGGTCAA**T**GAGCAA-3'

Fig. 10

Array Design for the R553X Point Mutation

Heterozygote Pattern



Wild-Type Sequence: 5'-AGGTCAA**C**GAGCAA-3'

Mutant Sequence: 5'-AGGTCAA**T**GAGCAA-3'

Fig. 11

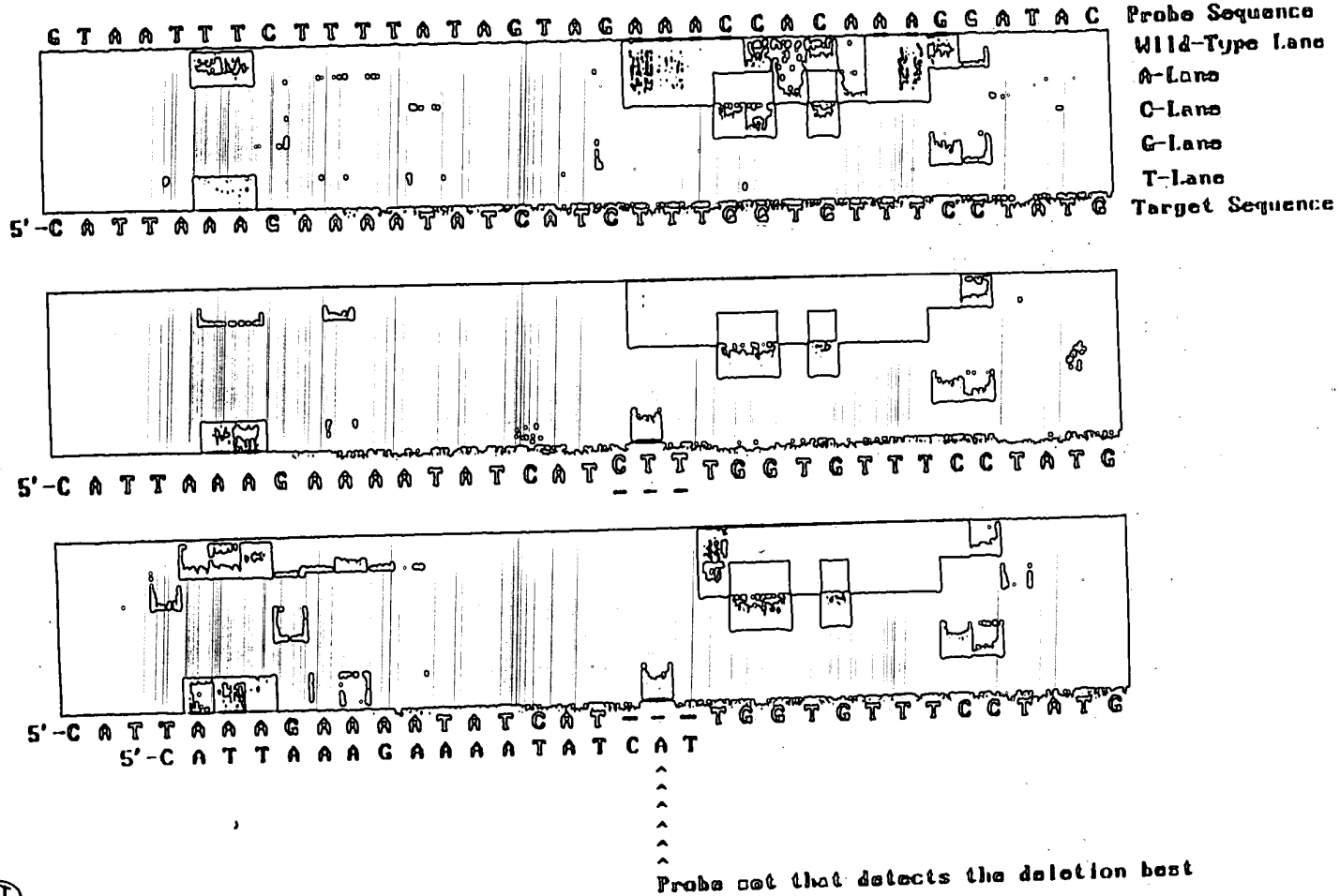
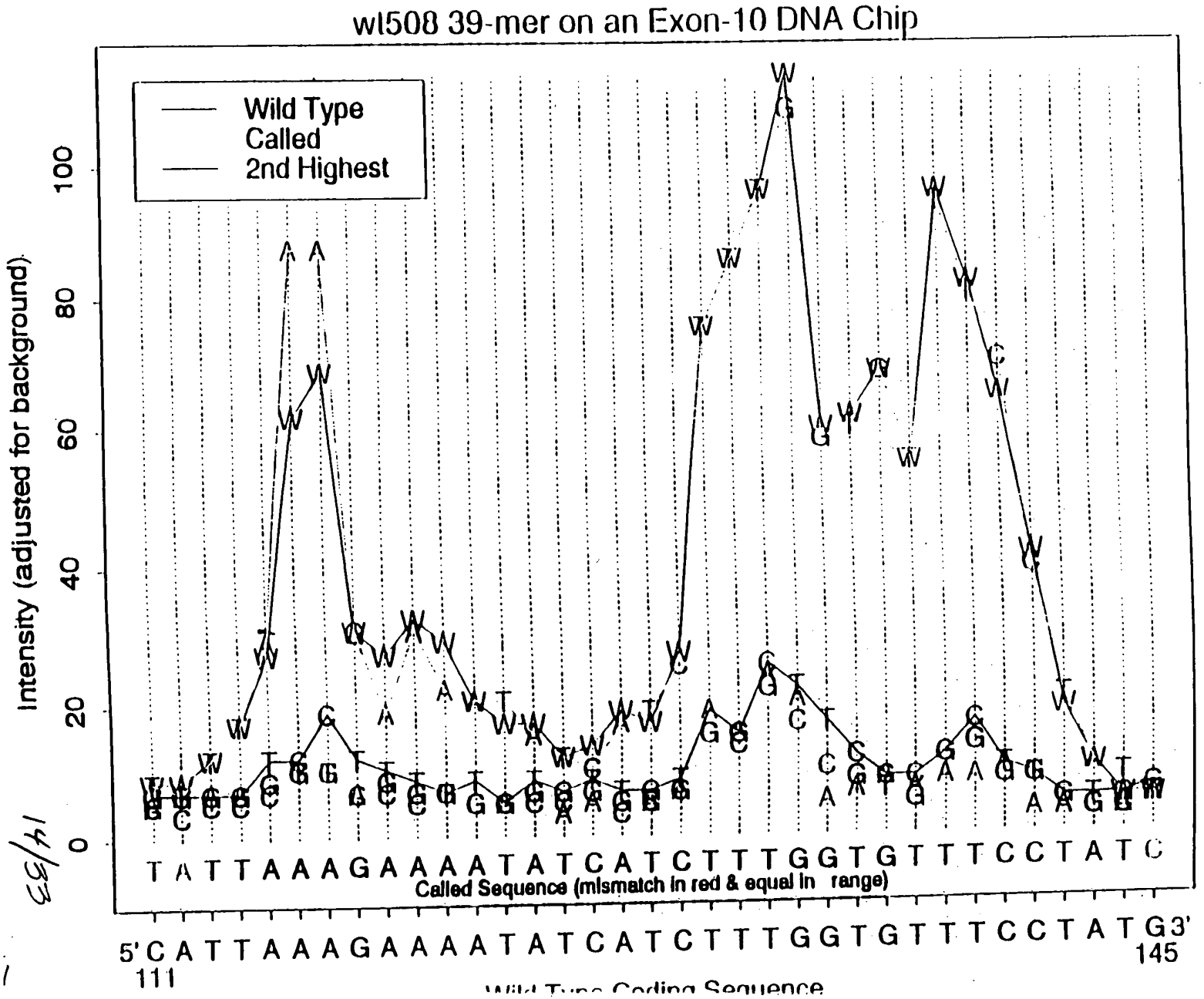
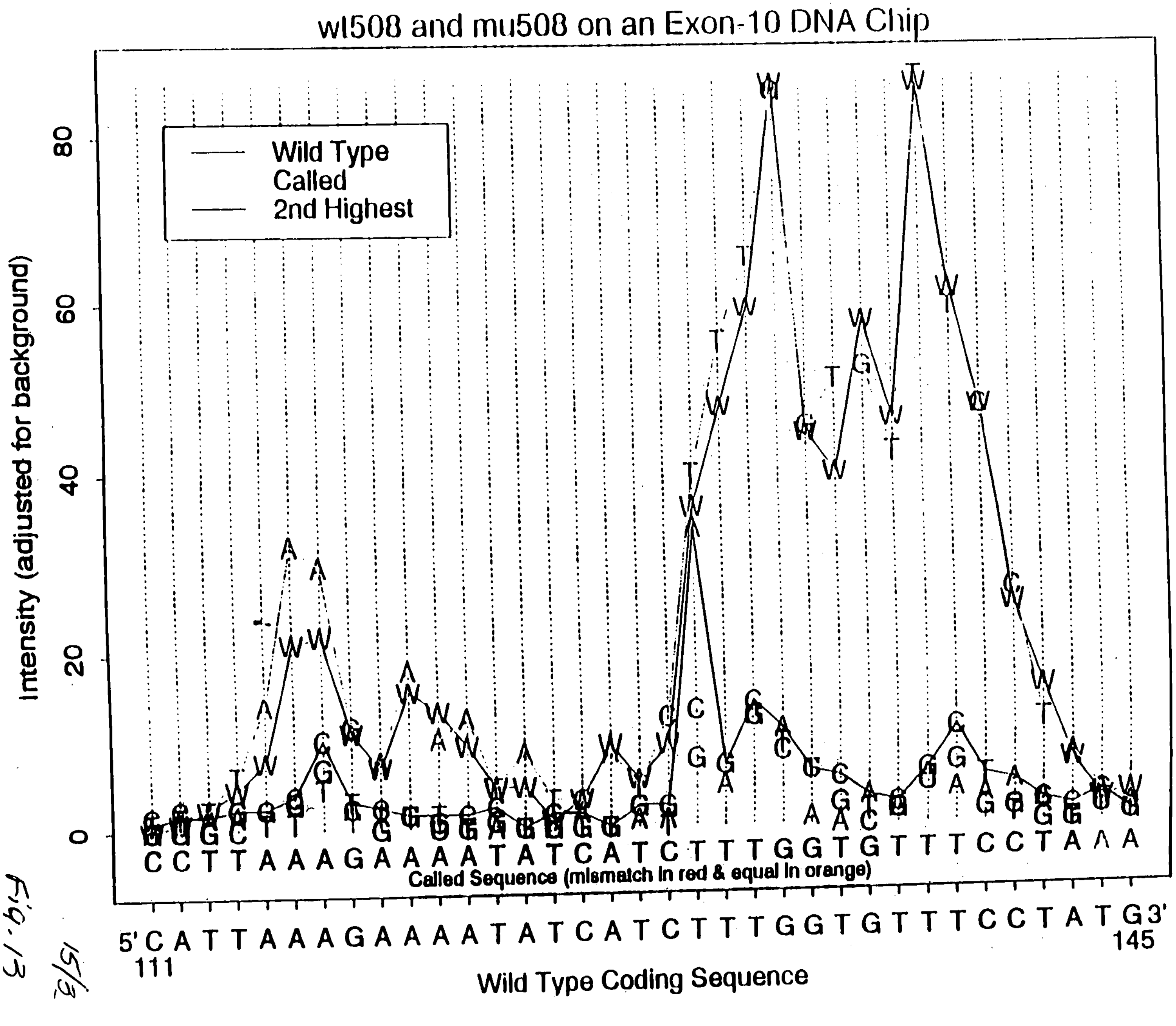

G T A A T T T C T T T T A T A G T A G A A A A C C A C A A A G G A T A C
Probe Sequence
Wild-Type Lane
A-Lane
C-Lane
G-Lane
T-Lane
5'-C A T T A A A G A A A A A T A T C A T C T T T G G T G T T T C C T A T G
Target Sequence
5'-C A T T A A A G A A A A A T A T C A T C T T T G G T G T T T C C T A T G
5'-C A T T A A A G A A A A A T A T C A T - - - T G G T G T T T C C T A T G
5'-C A T T A A A G A A A A A T A T C A T
Probe set that detects the deletion best

Fig. 12


wt508 39-mer on an Exon-10 DNA Chip
Wild Type Called
2nd Highest
Intensity (adjusted for background)
0
20
40
60
80
100
T A T T A A A G A A A A T A T C A T C T T T G G T G T T T C C T A T C
Called Sequence (mismatch in red & equal in range)
5' C A T T A A A G A A A A T A T C A T C T T T G G T G T T T C C T A T G 3'
111
145
Wild Type Coding Sequence


wl508 and mu508 on an Exon-10 DNA Chip
Wild Type
Called
2nd Highest
Intensity (adjusted for background)
0
20
40
60
80
C C T T A A A G A A A A T A T C A T C T T T G G T G T T T C C T A A A
Called Sequence (mismatch in red & equal in orange)
5' C A T T A A A G A A A A T A T C A T C T T T G G T G T T T C C T A T G 3'
111
145
Wild Type Coding Sequence

15/3

Fig. 13

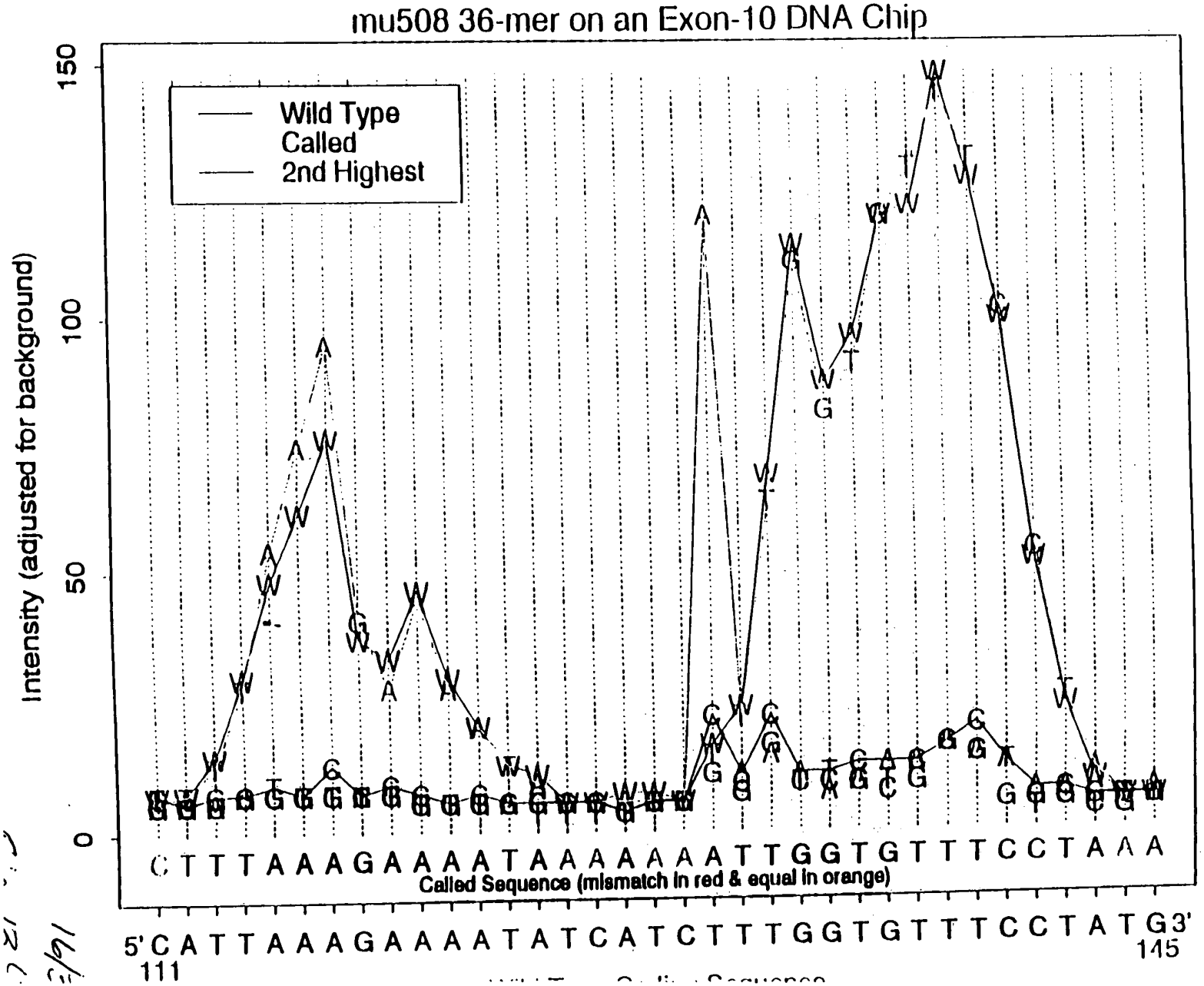
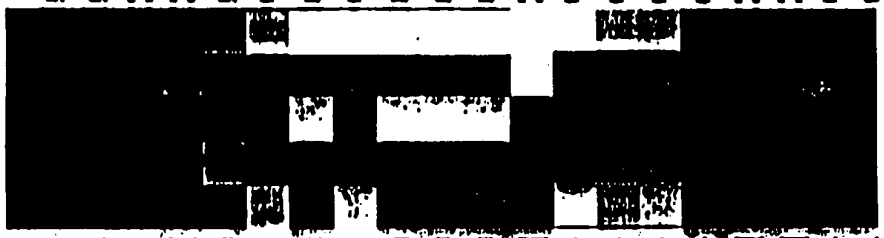

mu508 36-mer on an Exon-10 DNA Chip
Wild Type Called
2nd Highest
Intensity (adjusted for background)
0
50
100
150
C T T T A A A G A A A A T A A A A A A T T G G T G T T T C C T A A A
Called Sequence (mismatch in red & equal in orange)
5' C A T T A A A G A A A A T A T C A T C T T T G G T G T T T C C T A T G 3'
111
115

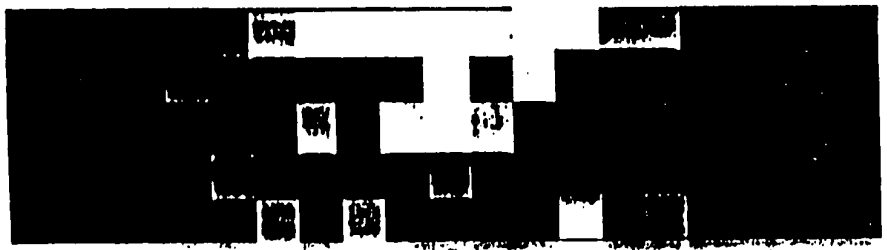
Fig. 14

A



Probe Sequence
Wild-Type Lane
A-Lane
C-Lane
G-Lane
T-Lane
Target Sequence

B



C

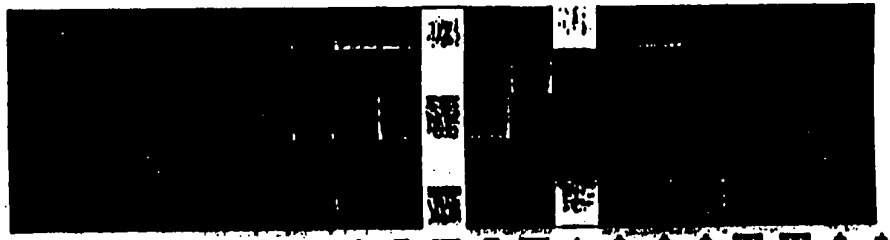


Fig. 15 (1 of 2)

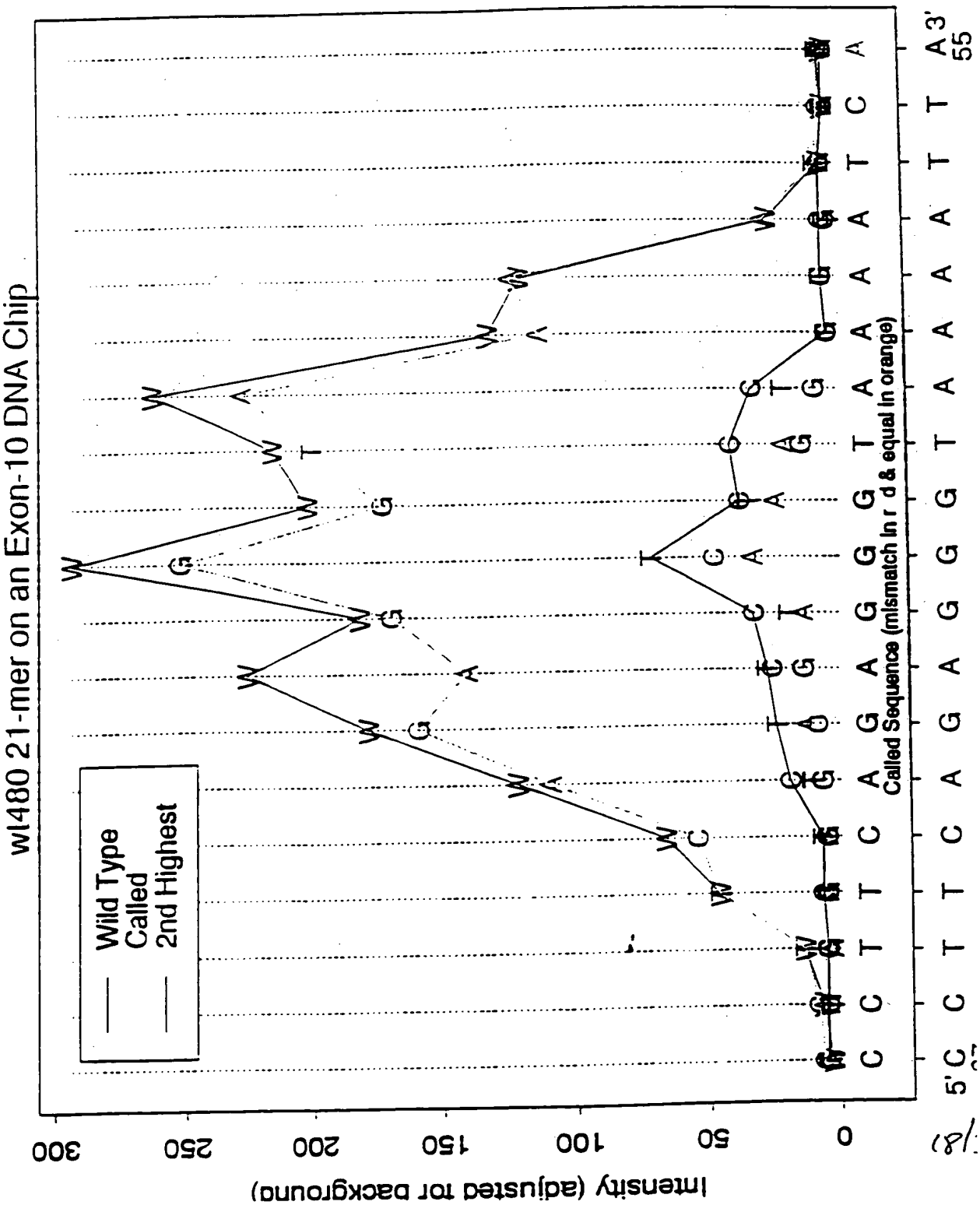
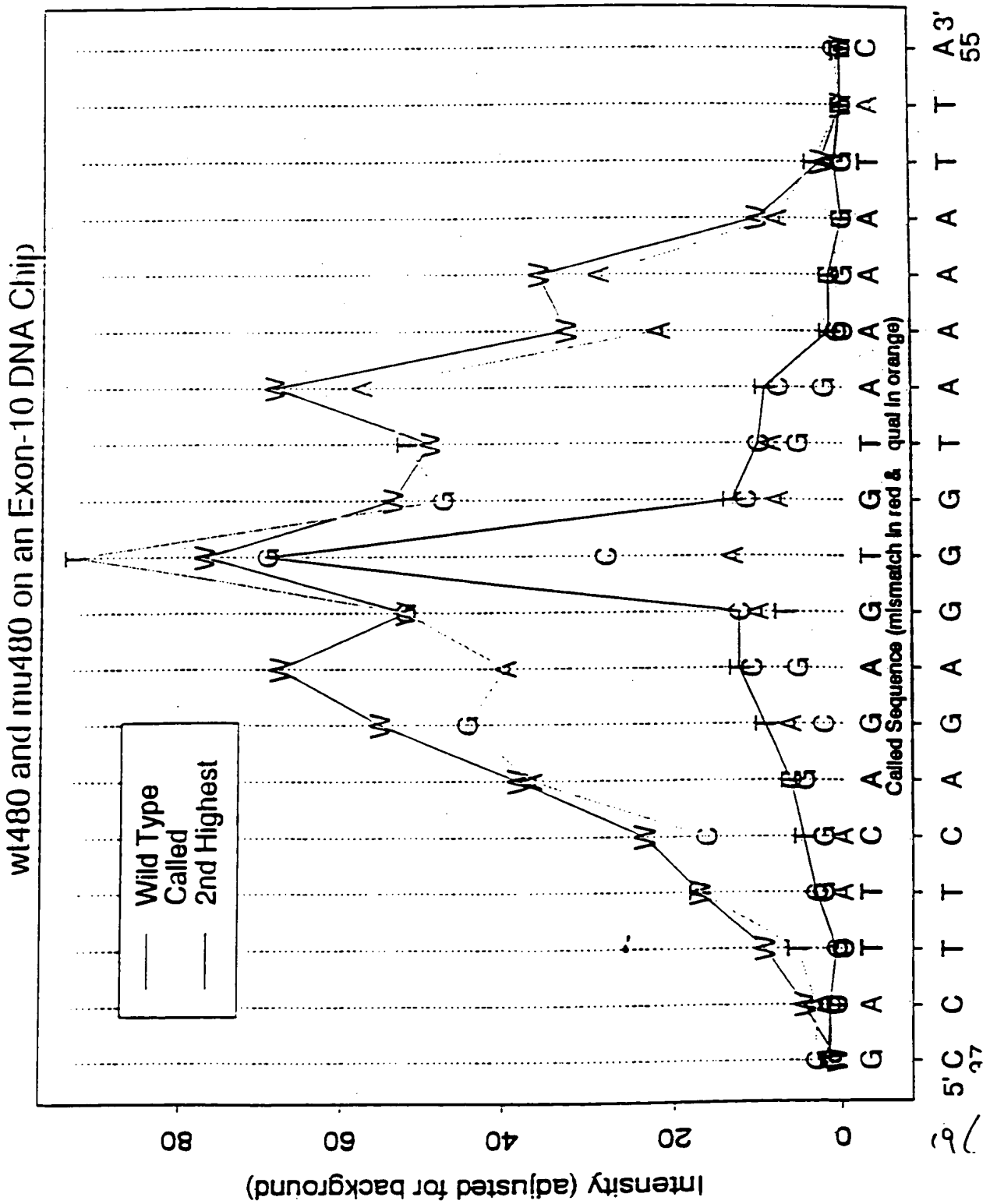

wt480 21-mer on an Exon-10 DNA Chip
Wild Type
Called
2nd Highest
Intensity (adjusted for background)
300
250
200
150
100
50
0
5'C C C T T C A G A G G G G T A A A A T T T C A A 3'
55
Called Sequence (mismatch in r d & equal in orange)

Fig 15 (2 of 3)


wt480 and mu480 on an Exon-10 DNA Chip
Wild Type Called
2nd Highest
Intensity (adjusted for background)
0
20
40
60
80
Called Sequence (mismatch in red & qual in orange)
5'C
A3'
27
55

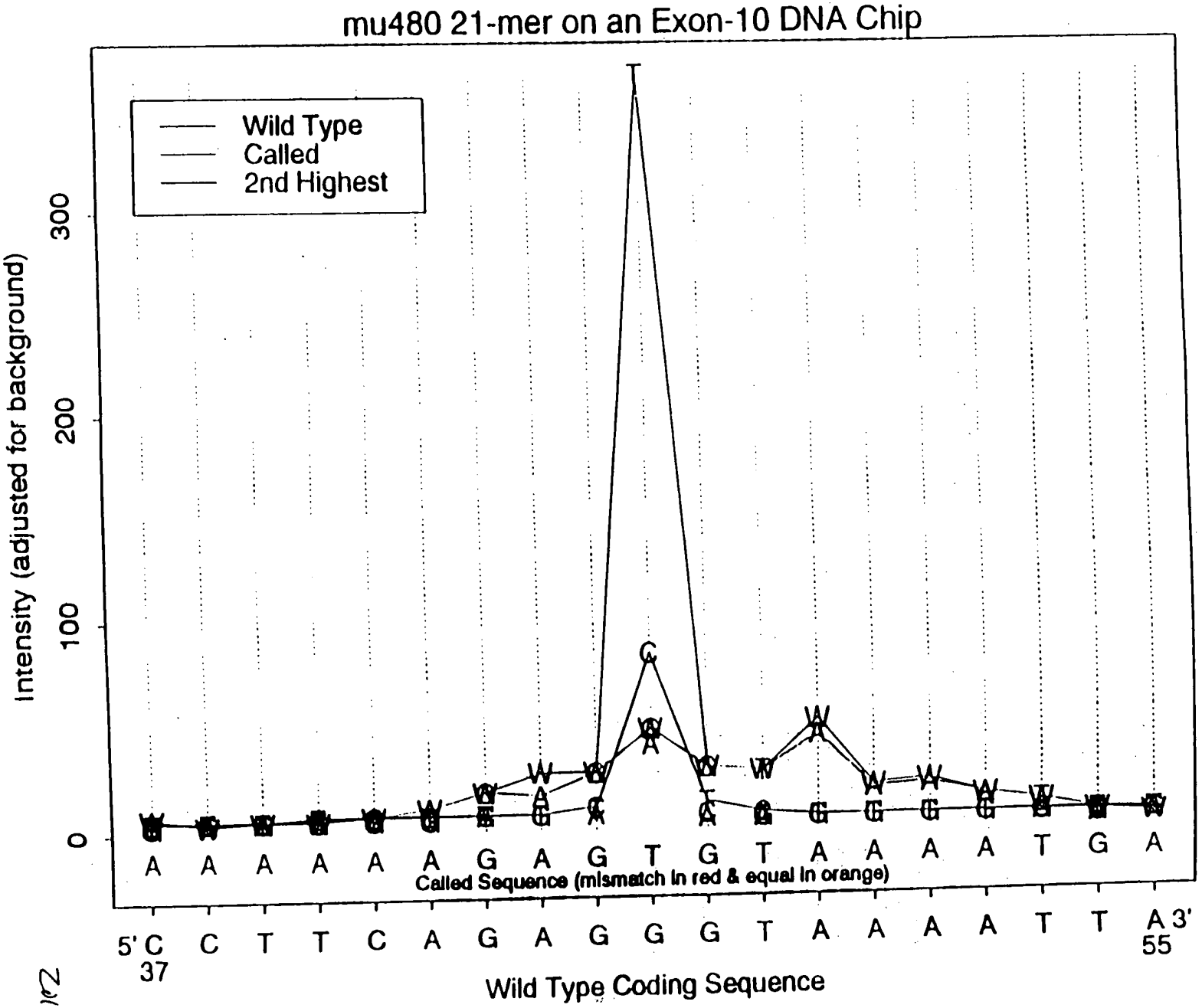

mu480 21-mer on an Exon-10 DNA Chip
Wild Type
Called
2nd Highest
Intensity (adjusted for background)
0
100
200
300
A A A A A A G A G T G T A A A A T G A
Called Sequence (mismatch in red & equal in orange)
5' C C T T C A G A G G G T A A A A T T A 3'
37
55
Wild Type Coding Sequence

Fig. 15 (3 of 3)

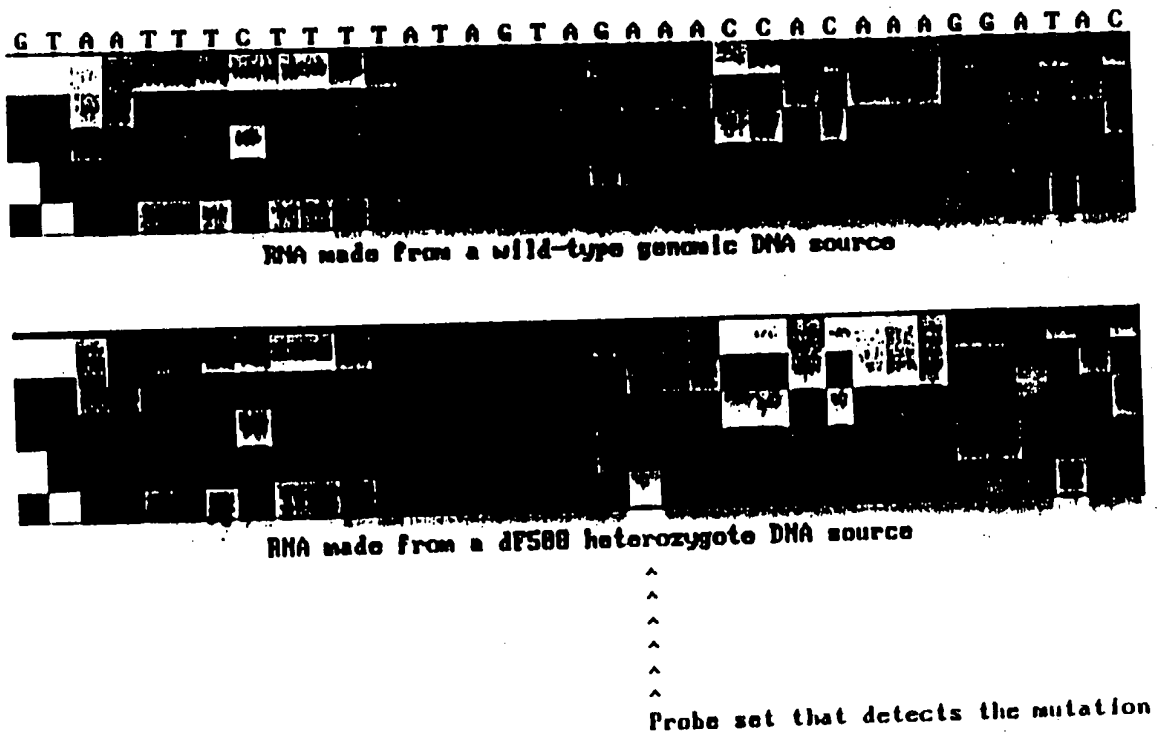


Fig. 16

Fig. 17 (1 of 2)

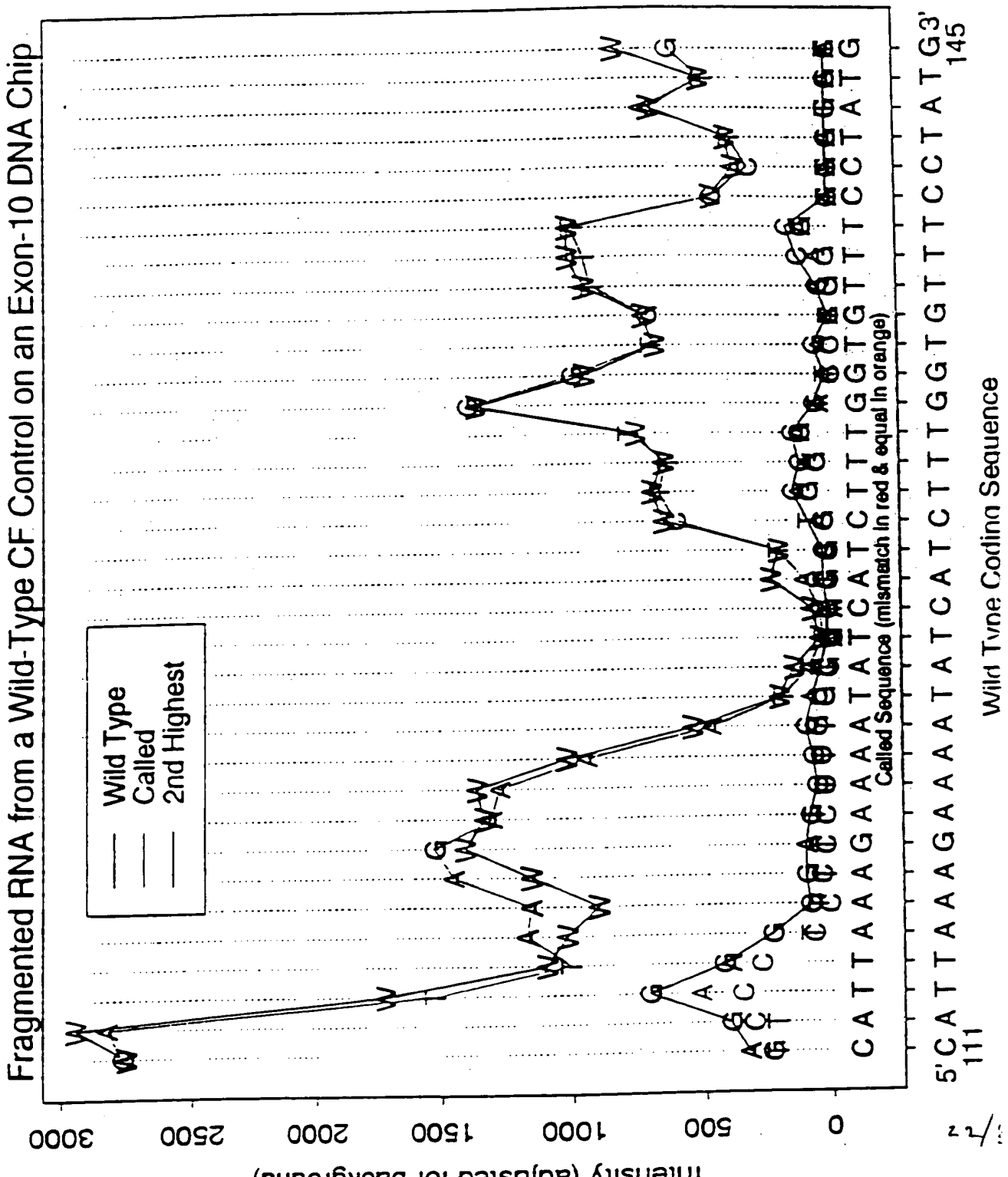
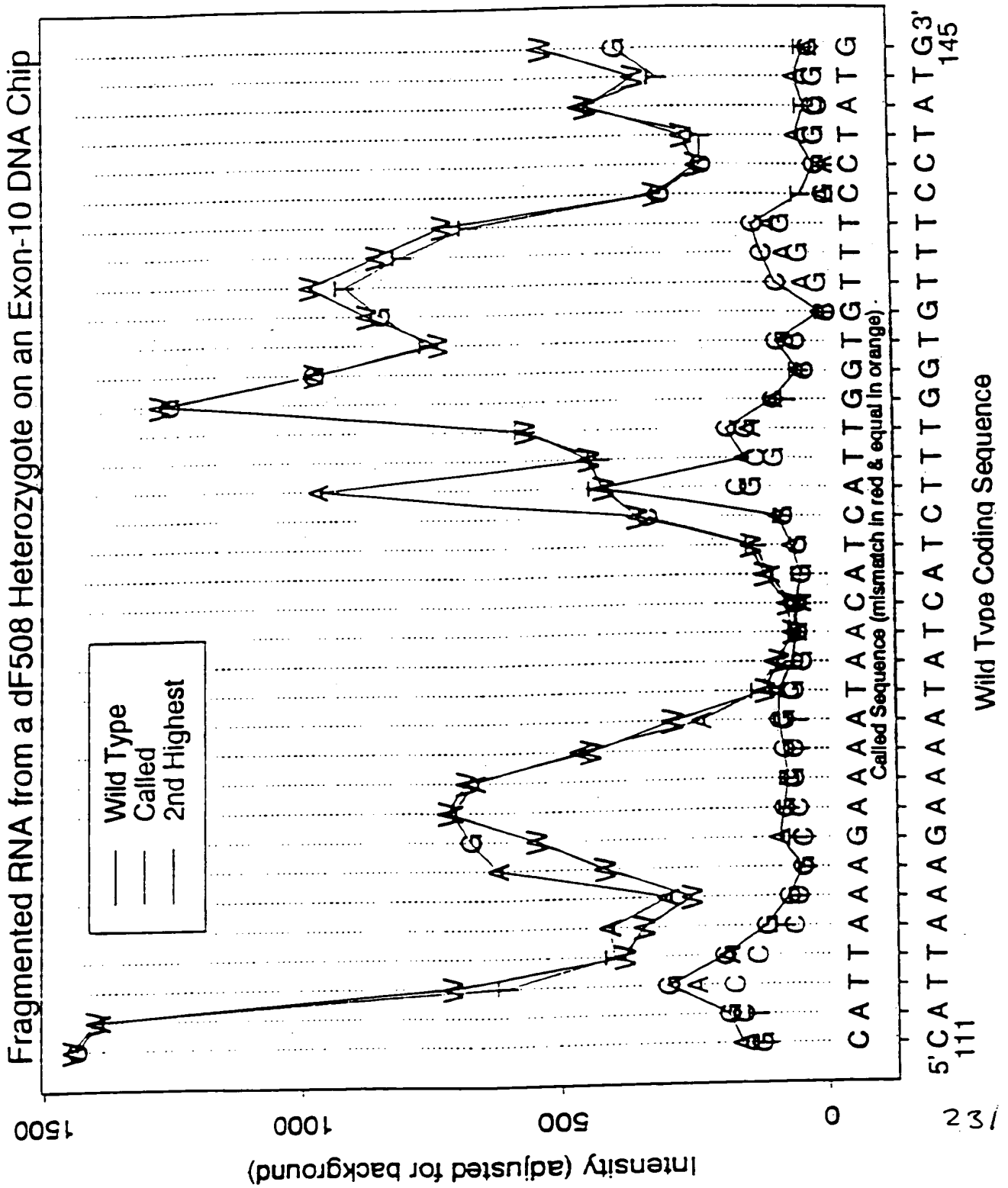
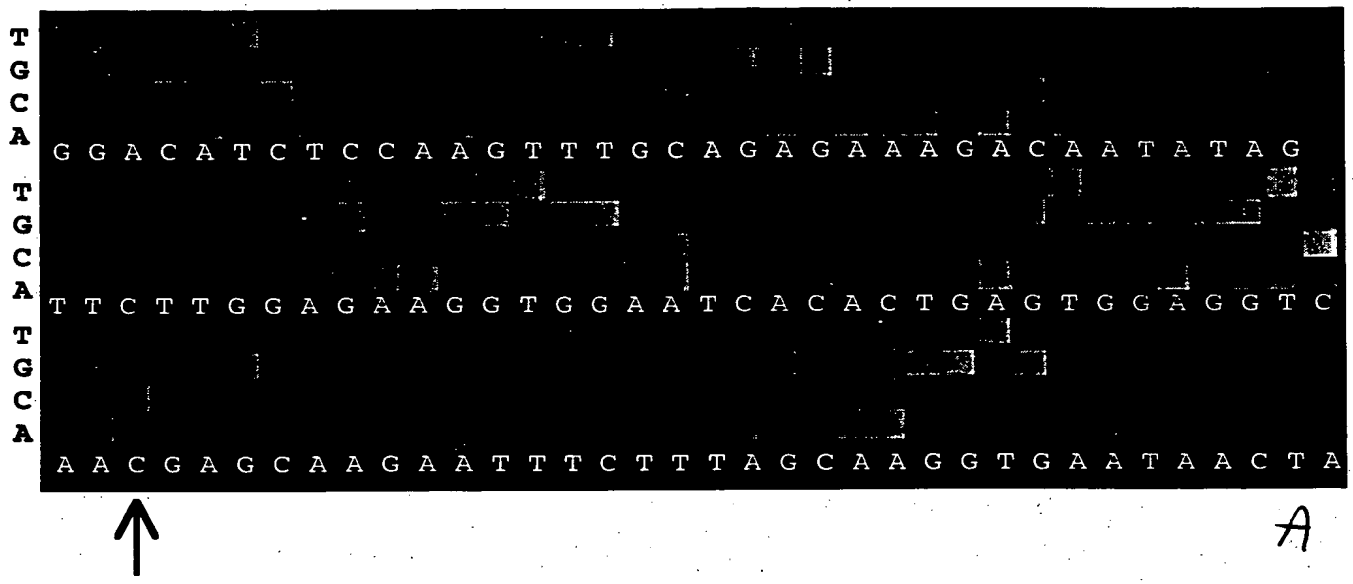
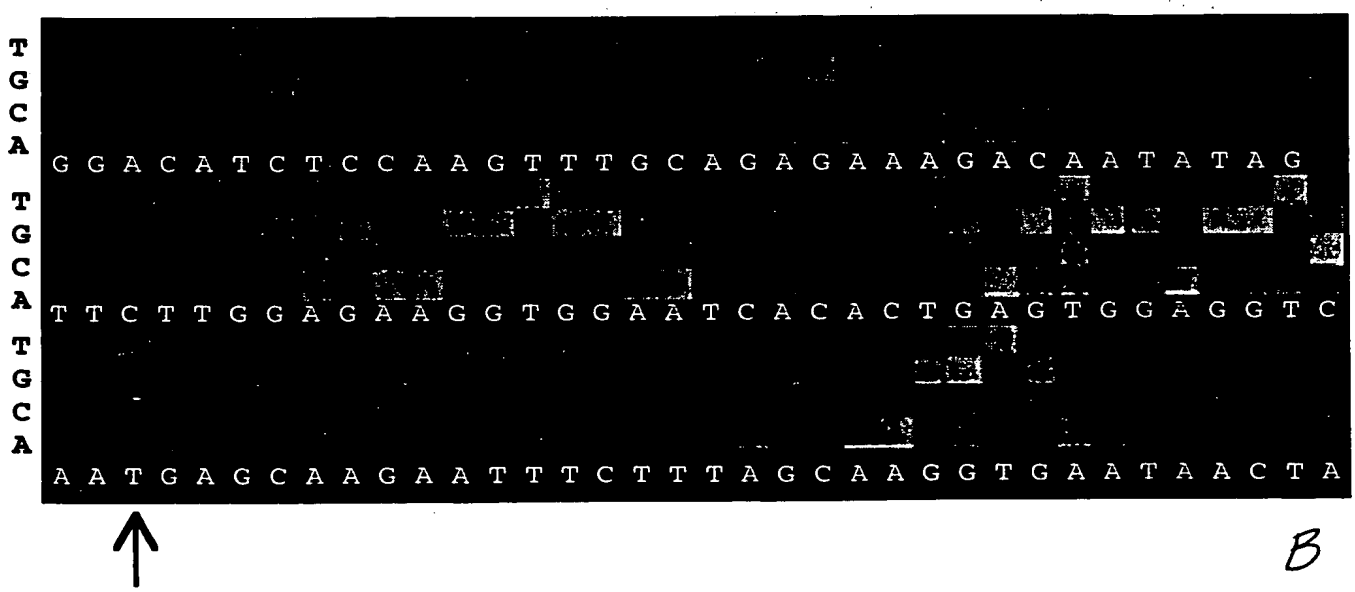

Fragmented RNA from a Wild-Type CF Control on an Exon-10 DNA Chip
Wild Type
Called
2nd Highest
Intensity (adjusted for background)
3000
2500
2000
1500
1000
500
0
5'
111
145
3'
Called Sequence (mismatch in red & equal in orange)
Wild Type Coding Sequence

Fig. 17 (2 of 2)


Fragmented RNA from a dF508 Heterozygote on an Exon-10 DNA Chip
Wild Type
Called
2nd Highest
Intensity (adjusted for background)
1500
1000
500
0
Called Sequence (mismatch in red & equal in orange)
5'CATTAAAGAAAATCATTGGTGTTTCCTATG3'
111
145
Wild Type Coding Sequence


TGCA
GGACATCTCCAAGTTTGCAGAGAAAGACAATATAG
TGCA
TTCTTGGAGAAGGTGGAATCACACTGAGTGGAGGTC
TGCA
AACGAGCAAGAATTTCTTTAGCAAGGTGAATAACTA

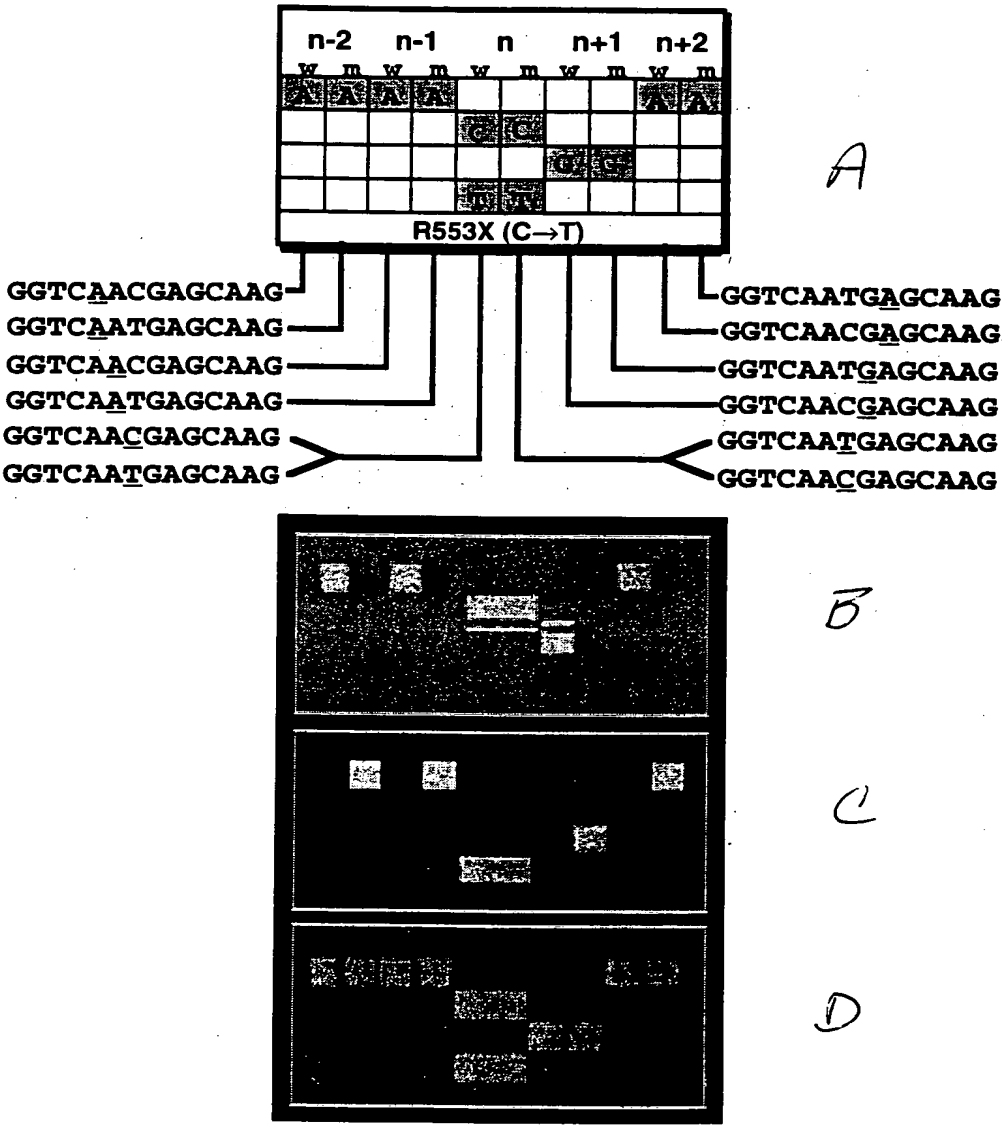
A


TGCA
GGACATCTCCAAGTTTGCAGAGAAAGACAATATAG
TGCA
TTCTTGGAGAAGGTGGAATCACACTGAGTGGAGGTC
TGCA
AATGAGCAAGAATTTCTTTAGCAAGGTGAATAACTA

B

Fig. 18

Fig. 19


n-2
n-1
n
n+1
n+2
w m w m w m w m w m
R553X (C→T)
GGTCAACGAGCAAG
GGTCAATGAGCAAG
GGTCAACGAGCAAG
GGTCAATGAGCAAG
GGTCAACGAGCAAG
GGTCAATGAGCAAG
GGTCAATGAGCAAG
GGTCAACGAGCAAG
GGTCAACGAGCAAG
GGTCAATGAGCAAG
A
B
C
D

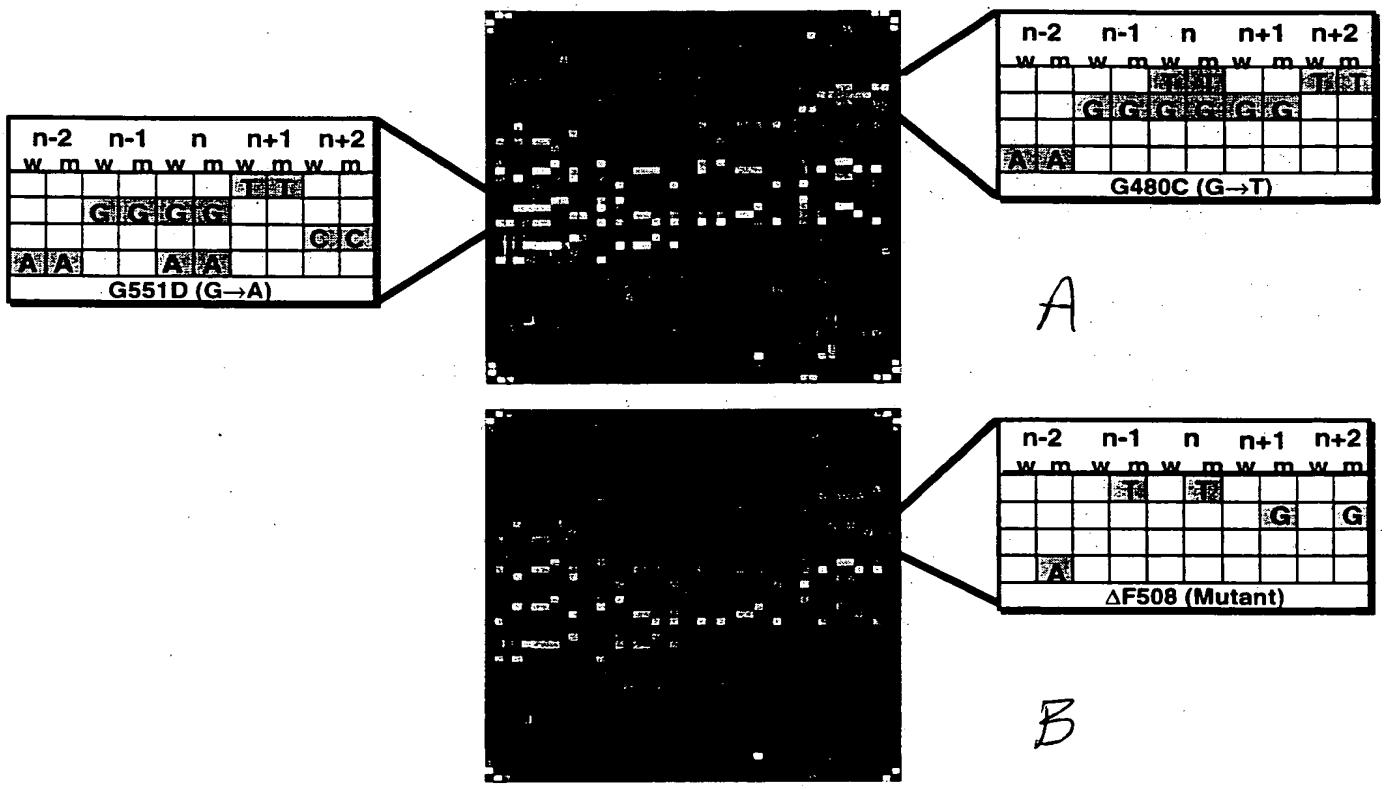

n-2 n-1 n n+1 n+2
w m w m w m w m w m
G551D (G→A)
n-2 n-1 n n+1 n+2
w m w m w m w m w m
G480C (G→T)
A
ΔF508 (Mutant)
B

Fig. 20

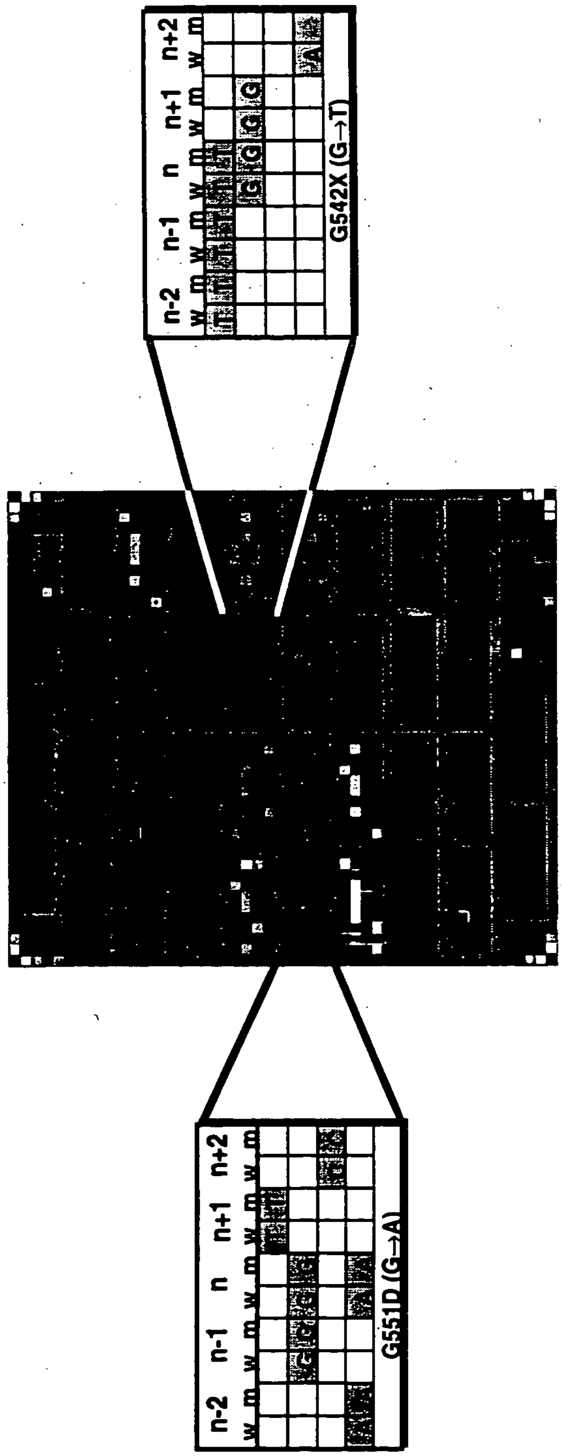

n-2 n-1 n n+1 n+2
w m w m w m w m w m
G542X (G→T)
n-2 n-1 n n+1 n+2
w m w m w m w m w m
G551D (G→A)

Fig. 21

ght Directed Oligonucleotide Synthesis

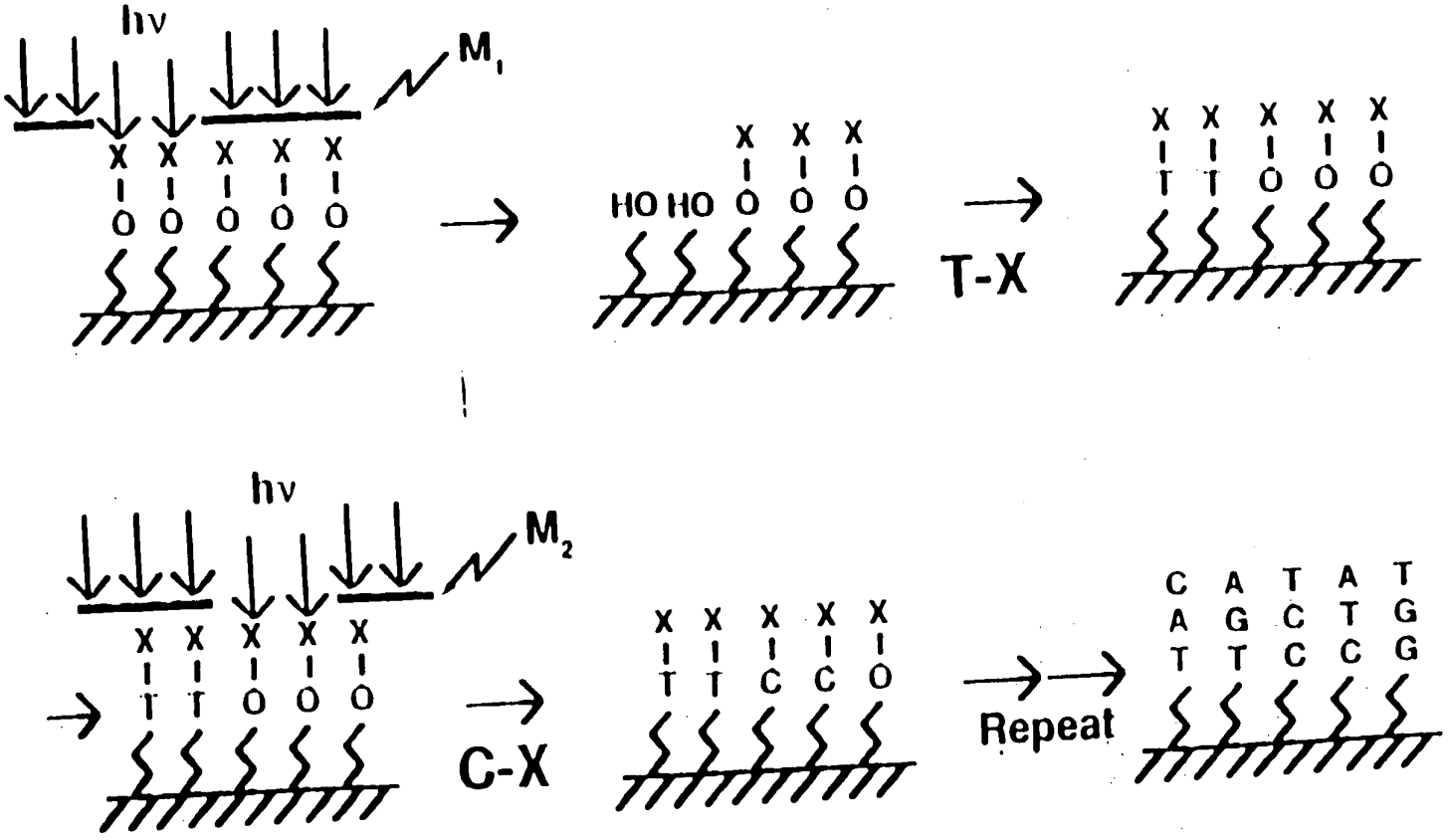
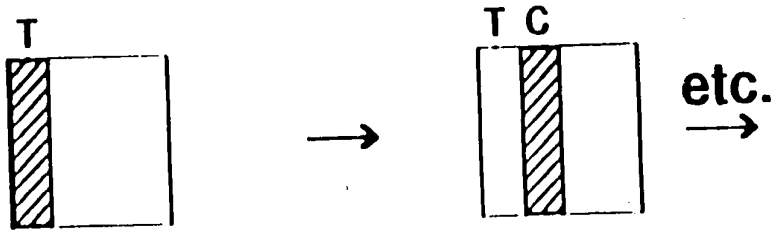
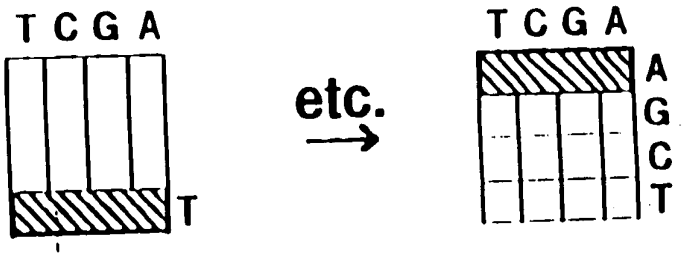


Fig. 22

lucleoside Combinatorials

Dimers:





in polynomial notation:

$(T + C + A + G)^2$ = All Dimers

Trimers:

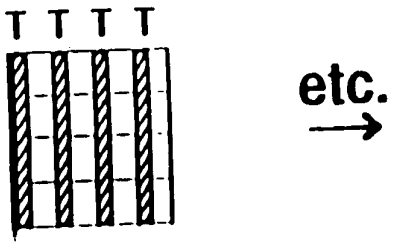
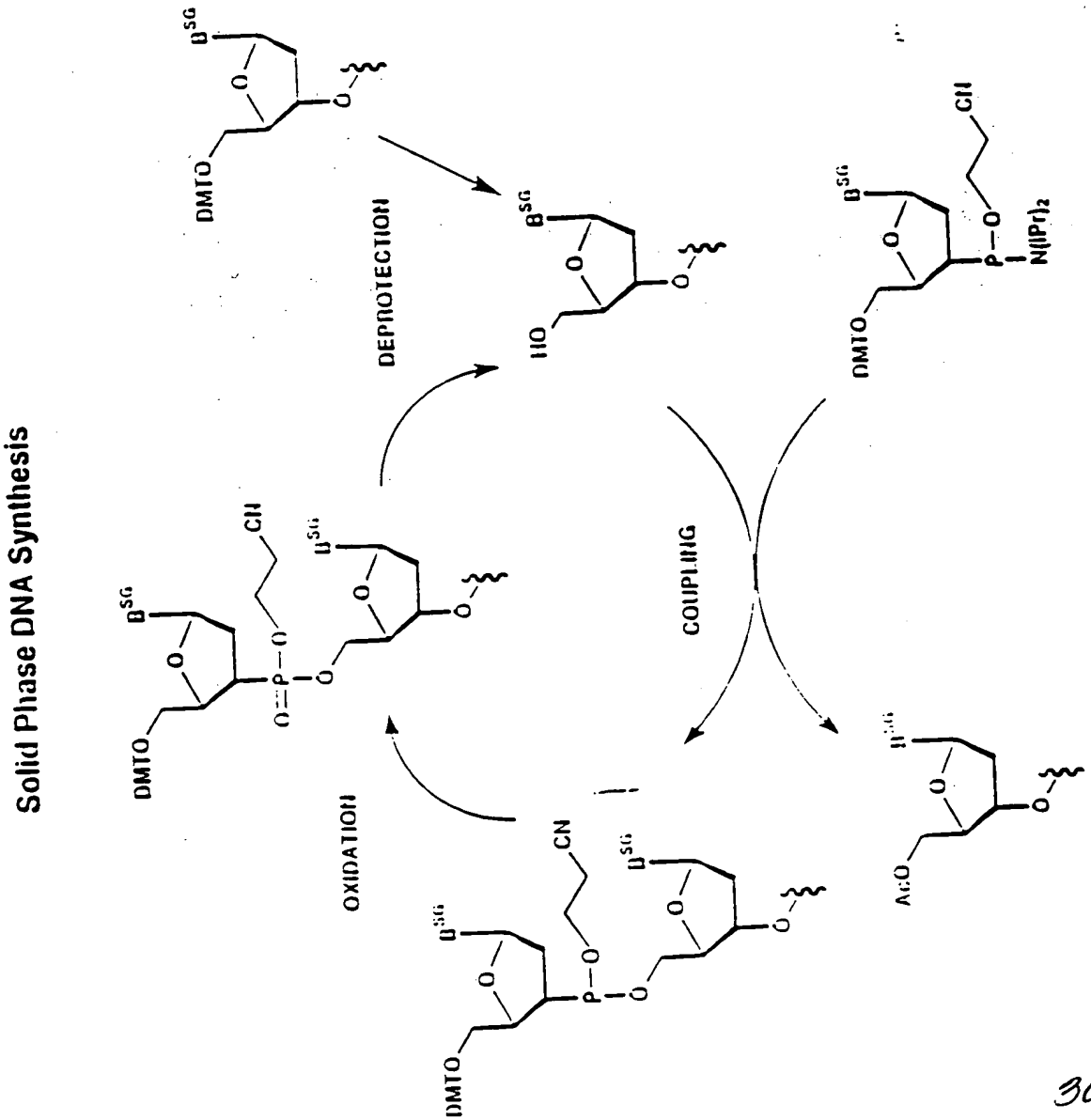
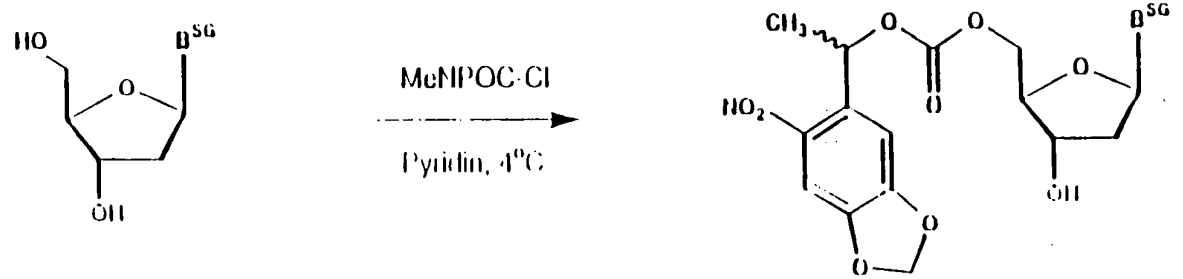


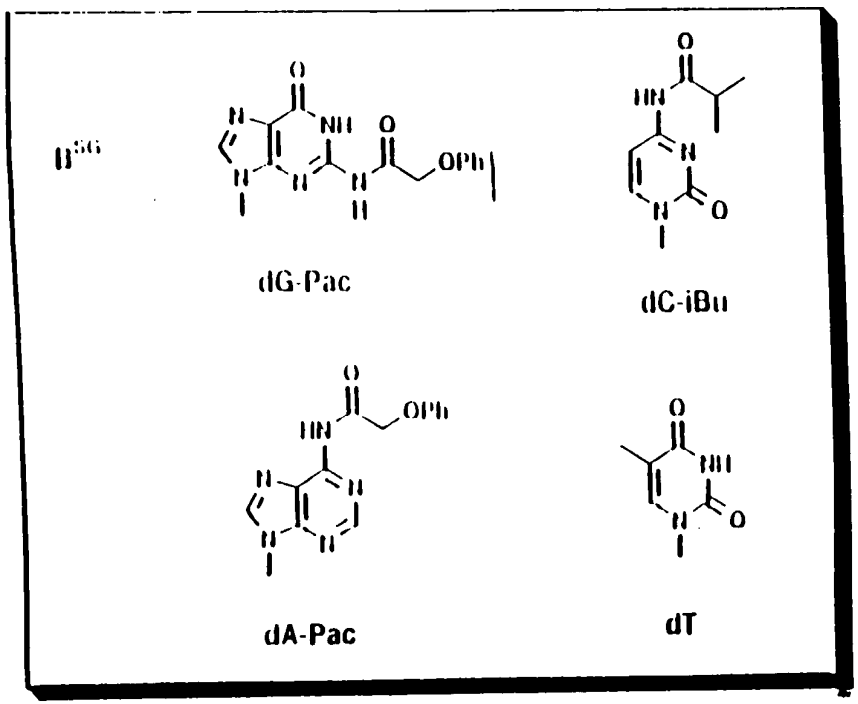
Fig. 23

Fig. 24


Solid Phase DNA Synthesis
DEPROTECTION
COUPLING
OXIDATION
DMTO
HO
AcO
CN
N(iPr)2

Nucleoside Buildingblocks





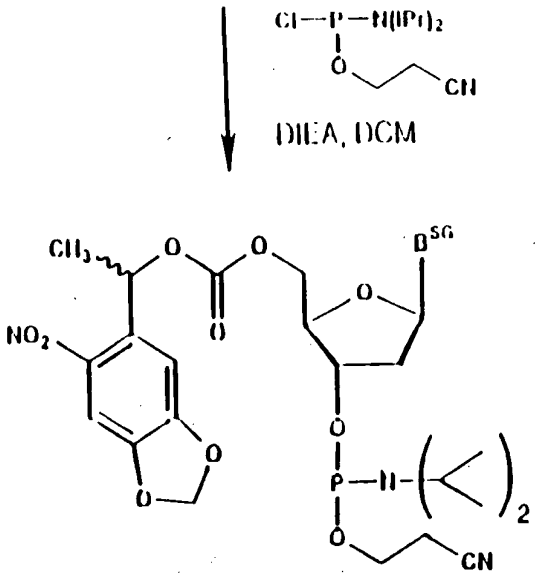


Fig. 25

MeNPOC-Cl

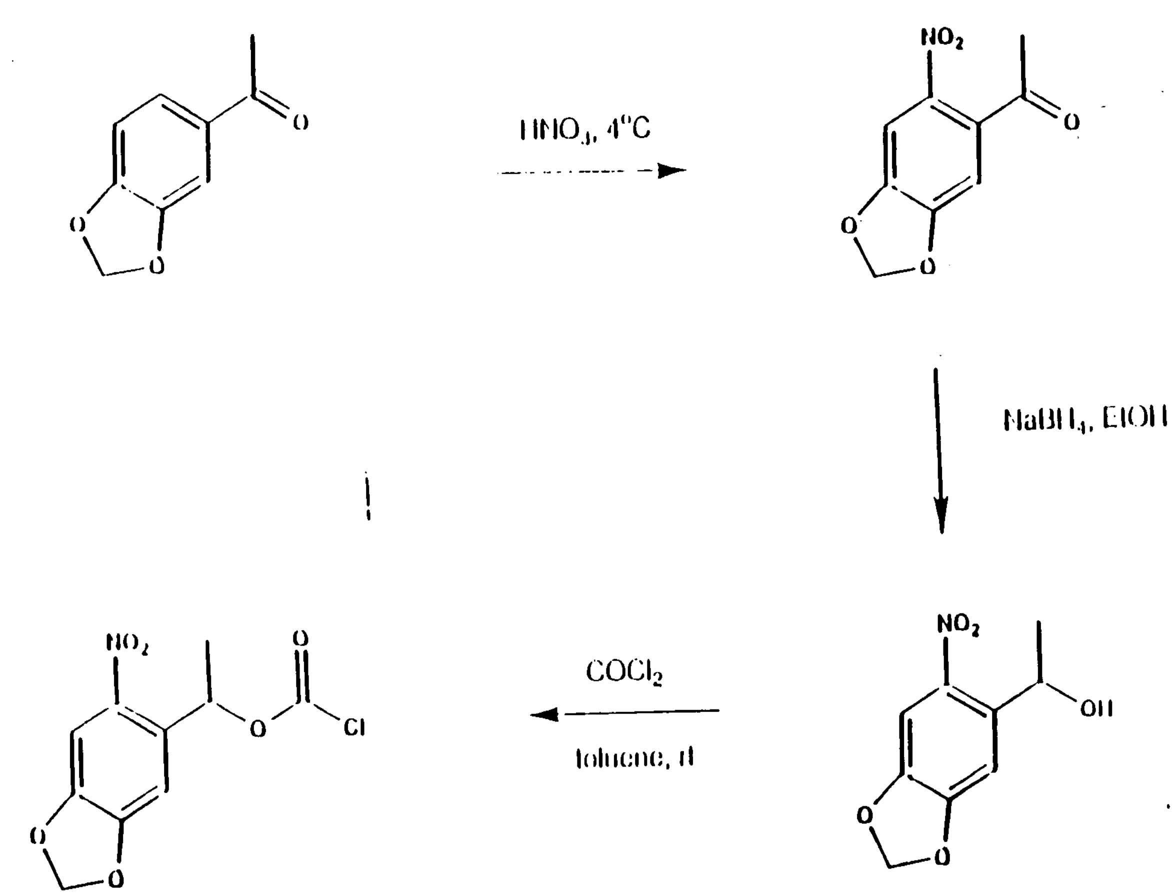


Fig. 26

Detection

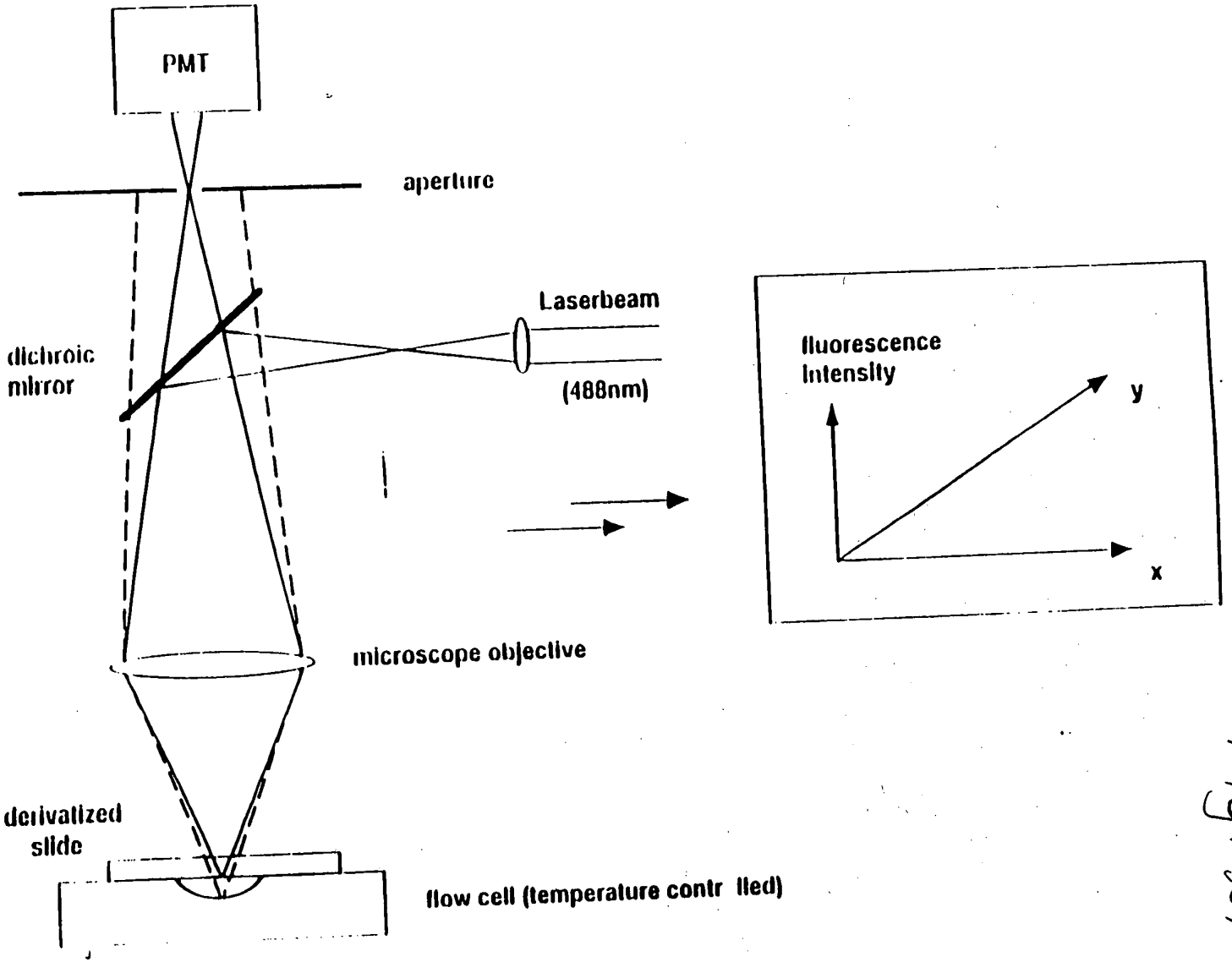


Fig. 27